

**Compare the efficacy of different antiplatelet therapy strategy
after Coronary Artery Bypass Graft Surgery**

(Study Number ISSBRIL0211)

Statistical Analysis Plan

(Version: 4.0)

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ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCS	Canadian Cardiovascular Society
CFDA	China Food and Drug Administration
CMH X2	Cochran–Mantel–Haenszel Chi-Squared Test
CRA	Clinical Research Associate
CRF	Case Report Form
CTA	Clinical Trial Agreement
DM	Data Management
EAP	Effective Analysis Population
EC	Ethics Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ITT	Intent to Treat
Max	Max
Mean	Mean
Median	Median
MedDRA	Medical Dictionary for Regulatory Activities
Min	Min
Missing	Missing
MSCTA	Multi-slice Spiral Computed Tomography Angiography
N	Number of Subjects (Number of Analysis Records)
OPCAB	Off pump Coronary Artery Bypass
PI	Principal Investigator
PLATO	Platelet Inhibition and Patient Outcomes
PP	Per-Protocol Set
SAE	Serious Adverse Event
SS	Safety Analysis Set
TIMI	Thrombolysis and Thrombin Inhibition in Myocardial Infarction
UCG	Ultrasonic Cardiogram

0、 Introduction

0.1 Background

For 30 years, antiplatelet therapy has been the gold standard for preventing saphenous vein graft closure after CABG. Aspirin is recognized as the standard of care and is generally continued indefinitely given its benefit in preventing subsequent clinical events. But 2010 Canadian guideline⁴ and 2012 Society of Thoracic Surgeons guideline⁵ recommended that in patients undergoing CABG after ACS, dual antiplatelet drugs should be restarted and that may have secondary benefit of increasing early vein graft patency. Hence, different antiplatelet therapy strategy after CABG is still in controversy.

However, as many as 50% of patients do not have adequate response to aspirin on the first postoperative day after cardiac procedures, and this percentage increases in the first week after operation, especially for off-pump procedures. Interestingly, the addition of clopidogrel did not seem to alter this nonresponse to aspirin. The clinical consequences of this lack of response remain uncertain, but evidence suggests lack of response to aspirin correlates with early vein graft closure after CABG and with recurrent cardiac events.

In patients with high residual platelet reactivity after the usual doses of clopidogrel, the novel antiplatelet agents are more effective at reducing platelet reactivity compared with increasing dose of clopidogrel. In the PLATO trial, ticagrelor, a novel reversible inhibitor of the P2Y₁₂ receptor, in addition to aspirin significantly reduced cardiovascular events in patients with ACS as compared to aspirin plus clopidogrel. The CABG substudy of the PLATO trial showed ticagrelor compared with clopidogrel was associated with a substantial reduction in total and CV mortality without excess risk of CABG-related bleeding.

0.2 Research Hypothesis

This study is designed to show the superiority of ticagrelor and ticagrelor plus aspirin as compared with aspirin monotherapy respectively for the 1-year primary efficacy end point of vein graft patency.

0.3 Rationale for Conducting this Study

For the study rationale, four recent published guidelines on CABG stated different antiplatelet therapy strategy for post-CABG is still in controversy. As 2010 ESC guideline on myocardial revascularization and 2011 ACCF/AHA Guideline for CABG recommended, aspirin monotherapy should be given to reduce the occurrence of vein graft closure and adverse cardiovascular events (Class I recommendation), but dual antiplatelet therapy is recommended (Class I) in 2010 Canadian guideline and 2012 society of thoracic surgeons guideline.

PLATO-CABG subgroup analysis showed that combination ticagrelor with aspirin is effective in this population, but it is still not clear which one will be more benefit for from dual antiplatelet or monotherapy as current controversy in patients receiving clopidogrel.

A systematically review showed that clopidogrel treatment alone demonstrate inferior with combination clopidogrel with aspirin in CABG patients.

Arterial graft patency rates are high even in the absence of antiplatelet therapy, the administration of antiplatelet therapy has not shown an improvement.¹⁵ In previous published literatures and datas in our center , compared with artery graft, vein graft patency rate is lower. Meanwhile, short-term(one year) stenosis or closure of vein graft is the main factor for thrombosis. So vein graft patency is an objective index for evaluating the effect of CABG postoperative.

0.4 Benefit/risk and Ethical Assessment

The Prescription Information for ticagrelor contains the information supporting the overall

risk/benefit assessment of the investigational agent and is available as a reference for investigators. It contains a summary of all the relevant pharmaceutical, nonclinical and clinical findings with ticagrelor.

Patients enrolled in this study will be treated with ticagrelor. Participation will entail recording of medical information about the patient in a confidential manner. Patient care will not be altered by participation. Ticagrelor will be provided to the subjects for free. The risks to patients include bleeding and dyspnoea, which are believed to be adequately handled in the clinical situation. The study will be approved by the local research ethics committee.

1、 Introduction to Study

1.1 Types of this Study

This is a phase IV, multi-center, open-label, active-controlled, randomized, parallel-group study.

1.2 Objective

The primary objective of this study will be to evaluate whether, as compared with aspirin monotherapy, ticagrelor plus aspirin and ticagrelor monotherapy could increase saphenous vein graft patency at 12 months after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography (CAG).

Secondary objectives including:

- 1) Saphenous vein graft patency at 7th day after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography (CAG).
- 2) Time to first event of major adverse cardiovascular event (MACE), composite of CV death, non-fatal myocardial infarction or non-fatal stroke (ischaemic or unknown etiology).
- 3) Rate of freedom from angina by questionnaire according to CCS classification at 12 months.
Rate of atrial fibrillation within 7 days post CABG.

1.3 Treatment Products in the Study

1.3.1 Recommendation for the Dosage of Ticagrelor and Aspirin

Ticagrelor: 90mg bid for 12 months

Aspirin: 100mg qd for 12 months

1.3.2 Doses and Treatment Regimens

Arm A: Aspirin 100mg qd for 12 months

Arm B: Ticagrelor 90mg bid plus Aspirin 100mg qd for 12 months

Arm C: Ticagrelor 90mg bid for 12 months

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study will be to evaluate whether, as compared with aspirin monotherapy, ticagrelor plus aspirin and ticagrelor monotherapy could increase saphenous vein graft patency at 12 months after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography (CAG).

2.2 Secondary Objectives

- 1) Saphenous vein graft patency at 7th day after surgery in the patients undergoing elective CABG, as assessed by multislice computed tomography angiography (MSCTA) or coronary angiography(CAG).
- 2) Time to first event of major adverse cardiovascular event (MACE), composite of CV death, non-fatal myocardial infarction or non-fatal stroke (ischaemic or unknown etiology).
- 3) Rate of freedom from angina by questionnaire according to CCS classification at 12 months.
Rate of atrial fibrillation within 7 days post CABG.

2.3 Safety Objective

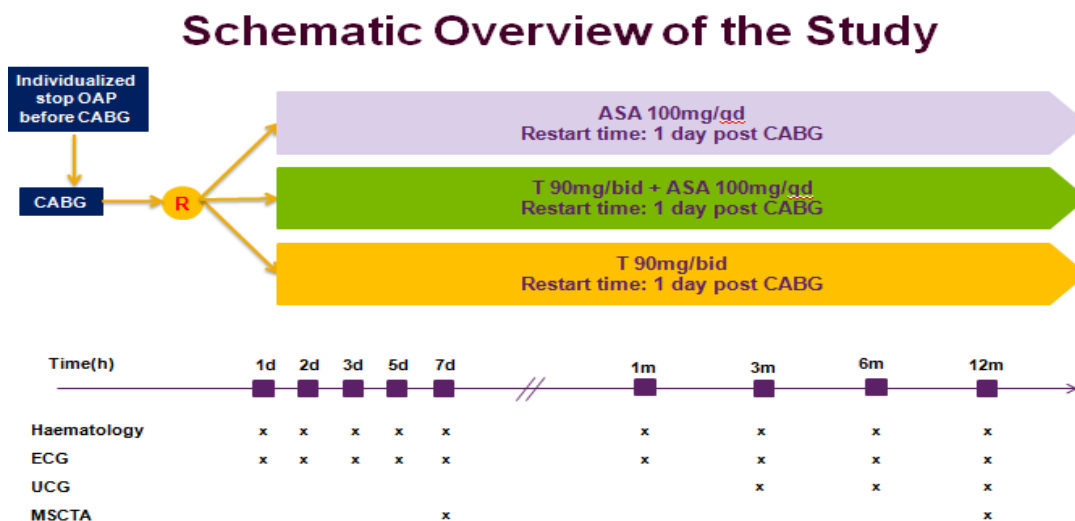
- 1) To compared with aspirin monotherapy, the major bleeding risk of ticagrelor plus aspirin and ticagrelor monotherapy according to Thrombolysis in Myocardial Infarction (TIMI) criteria.
- 2) Other adverse events (AEs) during the study

3. Study Design

3.1 Overall Study Design and Flow Chart

The study population will include all patients undergoing elective CABG. Consent and randomization will occur before surgery. Total 500 patients undergoing elective CABG will be randomly assigned into three groups with 1:1:1 ratio(167 patients per group) in this open-label study. All the enrolled patients will stop oral antiplatelet drugs according to local protocol before the surgery. Within the first 24 hours after surgery, study medication should be restarted and continued for 12 months. Arm A will restart oral antiplatelet drugs by giving aspirin 100mg qd, Arm B will also restart oral antiplatelet drugs by giving ticagrelor 90mg bid plus aspirin 100mg qd and Arm C will also restart oral antiplatelet drugs by giving ticagrelor 90mg bid. Treatment will continue for 12 months, at which time patients will undergo a multislice computed tomography angiography to assess vein graft patency.

3.2 Schematic Overview of the Study



3.3 Sample Size Justification

The trial was designed to compare rates of SV graft patency 1 year post CABG in patients randomized to ticagrelor plus aspirin combination therapy versus aspirin monotherapy, and in patients randomized to ticagrelor monotherapy versus aspirin monotherapy. The 1-year vein graft patency rate in the aspirin monotherapy group was assumed to be 90% in the ticagrelor plus aspirin group, 87% in the ticagrelor group and 80% in the aspirin group. The sample size calculations were performed with a 2-sided alpha level of 0.05 and 80% power. On the basis of these assumptions, a total of 199 SV grafts would be required in each group for the comparison of combination therapy versus aspirin monotherapy; and 441 grafts would be required in each group for the comparison of the 2 monotherapy groups. A total of 500 patients would be required to provide a total of 1350 to 1500 SV grafts, assuming that each patient would receive an average of 2.7 to 3.0 SV grafts.

3.4 Randomization and Blinding

3.4.1 Randomization after Subjects Enrolled

Patient eligibility will be established before treatment randomization. Patients will be enrolled/randomized strictly sequentially, as patients become eligible for enrolment/randomization. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

After providing informed consent, patients who are consistent with the inclusion and exclusion criteria will be randomly assigned to one of the three treatment groups. The randomization will be performed by a computer equally for the three treatment regimens. Each centre will be provided with sealed treatment code envelopes corresponding to a list of patient randomization numbers. Randomization numbers will be assigned strictly sequentially as subjects become eligible for randomization. When a subject is allocated to a specified randomization number, the corresponding code envelope will be opened to identify the allocated treatment regimen.

3.4.2 Blinding

This is an open-label study, so blinding is not applicable.

4. Study Endpoints

4.1 Evaluation Methods for Study Endpoints

- 1) The patency of vein grafts: assessed by multi-slice computed tomography angiography (MSCTA) or coronary angiography (CAG) according to Fitzgibbon Class
- 2) Recurrent angina: based on CCS Angina Class

4.2 Efficacy Endpoints

4.2.1 Primary Efficacy Endpoint

Angiographic vein graft patency by MSCTA or CAG at 12 months after CABG.

There are 3 levels of patency examination in vein grafts according to the Fitzgibbon Standards, that's level A, level B, and level O. The percentage of level A is the rate of vein graft patency.

Primary endpoint will be analyzed based on mFAS and PP.

4.2.2 Secondary Efficacy Endpoints

- 1) Angiographic vein graft patency assessed by MSCTA or CAG at 7th day post CABG.
- 2) In this study, MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (ischemic or unexplained). The rate of MACE and time to first MACE will be compared among 3 treatment groups.
- 3) Rate of recurrent angina will be compared among 3 treatment groups.
- 4) Rate of atrial fibrillation within 7 days post CABG. This rate is the percentage of subjects who had at least one PAF detected on electrocardiogram within 7 days post CABG. This rate will be compared among 3 treatment groups.

4.3 Safety Endpoints

- 1) Rate of adverse events
- 2) Rate of serious adverse events
- 3) Rate of adverse events leading to study agent interruption or withdrawal
- 4) Bleeding events will be defined according to TIMI standards (There are 2 types of bleeding events, CABG related bleeding and non-CABG related bleeding).
In this study, bleeding will also be compared among 3 treatment groups.

4.4 Other

- 1) Summary of the operation information, include the type of grafts, off-pump or on-pump CABG technique, etc.
- 2) Interested concomitant medication used, such as beta- receptor blockers, ACEI / ARBs, statins, and proton pump inhibitors
- 3) Rate of smoking at visit 9 (1 year after CABG)
- 4) Comparison in the chemistry and vital sign endpoints among 3 treatment groups
Rate of Glycated hemoglobin (HbA1c) $\geq 6.5\%$ from visit 6 to visit 9;
Rate of Glycated hemoglobin (HbA1c) $\geq 7.0\%$ from visit 6 to visit 9;
Rate of Low-density lipoprotein ≥ 1.8 mmol/L from visit 6 to visit 9;
Rate of Low-density lipoprotein ≥ 2.6 mmol/L from visit 6 to visit 9;
Rate of Systolic blood pressure ≥ 140 or Diastolic blood pressure ≥ 90 mmHg from visit 6 to visit 9.

5, Data Management

A quality assurance audit/inspection of this trial may be conducted by AstraZeneca or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

6. Analysis Specifications

6.1 Adverse Events

6.1.1 AE Duration

AE duration is in days:

Duration = end date – start date + 1 (days)

6.1.2 Imputation of Missing AE Data

1. Severity

If the severity is missing, then “severe” will be imputed.

2. Relationship

If the relationship is missing, then “very likely” will be imputed.

6.2 Concomitant Medication

Imputation won't be applied to concomitant medication data.

6.3 Age Calculation

Age of subjects will be calculated based on the date of visit 1, and in years, the formula is:
(date of visit 1 – birthday + 1) ÷ 365.25

7. Analysis Sets

This study will be analyzed by the planned treatment, regardless the actual treatment this subject received.

7.1 Intent to Treat (ITT)

ITT will include all the subjects who were randomized.
Demographic and baseline data will be analyzed on ITT.

7.2 Modified Full Analysis Set (mFAS)

All the subjects in ITT will be included in mFAS, except those subjects who didn't take any study agent or withdraw ICF before the first dose of study agent.
All the efficacy analysis will be based on mFAS.

7.3 Per Protocol Set (PPS)

The subjects in mFAS who have no drug discontinuation or drug discontinuation ≤ 60 days, have

no other major protocol deviation, didn't take any forbidden concomitant medication, have the primary endpoints assessment at 1 year post-CABG will be included in PPS.

PPS will only be used in primary endpoint sensitive analysis.

7.4 Safety Analysis Set (SS)

All the subjects who took at least one study agent will be included in safety analysis set.

Safety endpoints, such as adverse events, bleeding events, laboratory test, vital sign, will be analyzed based on safety analysis set.

8. Statistical Analysis Methods

This part contains general and specific definitions of statistical methods for the analysis of collected data in this study, however, any post-hoc analyses performed that are different from this part, will be documented in the analyses section of the CSR.

8.1 Statistical Analysis Software

All the statistical analyses are done on SAS 9.3 (SAS Institute Inc.).

8.2 General Statistical Analysis Methods Applied

Unless otherwise stated, statistical significance level is set to 0.05 (2-sided).

8.2.1 Continuous Variables

Descriptive summary statistics, such as number of subjects, mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum will be used for continuous variable.

ANOVA or Kruskal-Wallis test will be applied to the statistical test in the homogeneity of distribution among these 3 treatment group, whether ANOVA or Kruskal-Wallis test is determined by the tests of normality distribution and homogeneity of variance with the alpha level 0.05 for this variable.

8.2.2 Discrete Variables

Counts and percentages will be used to summarize the discrete variables. Fisher exact test, Continuity Adjusted Chi-Squared test, or Pearson Chi-Squared test will be applied to test homogeneity of the rates among 3 treatment groups, the choice on the method will be based on the actual counts in the frequency cells.

8.2.3 Ordinal Variables

Counts and percentages will be used to summarize the ordinal variables. Kruskal-Wallis test will be used in the comparison of ordinal variables.

8.3 Statistical Test for Primary Endpoint

The primary endpoint is the patency rate of vein grafts at visit 9 (1 year after CABG). Generally, there will be 1 to 4 grafts be examined per a subject, this is a typical repeated measures data, since those grafts within a subjects are definitely correlated, the conventional statistical methods like Pearson Chi-Squared test isn't appropriate to test primary endpoint in this study. GEE (Generalized Estimating Equation) [1] is used to test the hypothesis of this study, 95% CIs and 2-sided p values will be provided.

8.3.1 Handling in Missing Values for Primary Endpoint

If the patency examination for a graft at the visit 9 (1 year after CABG) is missing, then level O will be imputed, then this graft is deemed as occlusion in primary analysis.

8.3.2 Statistical Test for Primary Endpoint

$$H_0 : P_T - P_A = 0 \quad H_1 : P_T - P_A \neq 0 \quad \text{与} \quad H_0 : P_{T+A} - P_A = 0 \quad H_1 : P_{T+A} - P_A \neq 0$$

A—Aspirin、T—ticagrelor、T+A—Aspirin + ticagrelor

Patency results from all the 3 treatment groups will be modeled in a same Generalized Estimating Equation, the rate difference and its 95% CI will be derived for the comparisons of A vs A+T (or A vs T). If the lower of 95% CI is greater than 0, then A+T (or T) is statistical significantly higher in the patency rate than A, the superiority of A+T (or T) proved.

8.3.3 Statistical Descriptive of Patency of Grafts

There levels of patency examination in grafts according to the Fitzgibbon Standards, that's level A, level B, and level O, and it's ordinal variable. The patency of grafts at the visit 5 (7 days after CABG) and visit 9 (1 year after CABG) will be summarized by using the statistical method for the ordinal variable.

8.4 Secondary Endpoints

8.4.1 Handling in Missing Values for Secondary Endpoint

For the missing values in the patency examination for any graft in any visit will be imputed by the worst level in Fitzgibbon Standards.

For the other secondary endpoints, missing value won't be imputed.

8.4.2 Statistical Descriptive and Statistical Test for Secondary Endpoints

GEE will be applied to the rate of patency and non-occlusion of grafts, the other secondary endpoints will be analyzed by using the statistical methods defined in chapter 8.2, depends on the property of the variables.

For MACE, statistical methods for the discrete variables will be applied to compare the rates of MACE event among these 3 treatment groups, Time to MACE (measured in days) will be analyzed using a log-rank test. Subjects who had not experienced MACE will be right-censored. The survival curves will be estimated using Kaplan-Meier estimates.

8.5 Safety Endpoints

8.5.1 Adverse Events

AEs that occurred any time over the study will be reported and coded using Medical Dictionary for Regulatory Activities (MedDRA). All the adverse events will be listed. AEs will be summarized by treatment group, system organ class and preferred term.

The following AE summary tables will be provided for this study:

- Adverse event
- Serious adverse event (SAEs)
- AEs leading to study agent interruption or withdrawal

8.5.2 Smoking

The comparison of smoking status in these 3 treatment groups will be analyzed by using the statistical methods for the discrete variable

8.5.3 Bleeding Events

The rate of bleeding events (Major bleeding, CABG related bleeding, non CABG related bleeding) among these 3 treatment groups will be summarized by using the statistical method for discrete variable.

8.5.4 Comparison in the Chemistry and Vital Sign Endpoints among 3 Treatment Groups

Rate of Glycated hemoglobin (HbA1c) $\geq 6.5\%$ from visit 6 to visit 9

Rate of Glycated hemoglobin (HbA1c) $\geq 7.0\%$ from visit 6 to visit 9

Rate of Low-density lipoprotein ≥ 1.8 mmol/L from visit 6 to visit 9

Rate of Low-density lipoprotein ≥ 2.6 mmol/L from visit 6 to visit 9

Rate of Systolic blood pressure ≥ 140 or Diastolic blood pressure ≥ 90 mmHg from visit 6 to visit 9

The above comparisons will be analyzed by using the statistical methods for the discrete variable.

8.6 Other Variables

8.6.1 Demographic and Baseline Data

Demographic and baseline characteristic variables will be descriptively summarized in ITT, no formal statistical comparison is planned.

8.6.2 Baseline and Medical History

The collected baseline data and medical history included angina, (CCS angina grade), history of myocardial infarction, New York Heart Association (NYHA) functional classification, history of cerebrovascular accident; history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of chronic obstructive pulmonary disease (COPD), history of peptic ulcer or digestive hemorrhage, history of chronic kidney disease (CKD) (defined as baseline creatinine > 200 μ mol/L), history of peripheral arterial disease (PAD) (defined as a stenosis $\geq 50\%$ detected in any carotid or femoral artery by Doppler ultrasonography), history of smoking, results of ultrasonic cardiogram (LVED, LVEF), SYNTAX score, EuroScore, and preoperative concomitant medication (including aspirin, IIb/IIIa antagonist, low molecular weight heparin, beta blocker, ACEI / ARB, statin and proton pump inhibitor).

8.6.3 Operation Information Data

Operation information data including type of total grafts, number of IMA grafts RA grafts and SV grafts; off-pump or on-pump were collected as categorical variables.

8.6.4 Concomitant Medication

The proportion of patients using concomitant medication was collected at each follow-up point and was compared among the three groups. Main concomitant medications included beta blocker, ACEI / ARB, statin and proton pump inhibitor, comparative statistical analysis was carried out in each medication.

8.7 Interim Analysis

No interim analysis for this study.

References

- [1]. Liang, K. Y. and Zeger, S. L. (1986), “Longitudinal Data Analysis Using Generalized Linear Models,” *Biometrika*, 73, 13–22.

Appendix: Time and Events Schedule

Phase	Base line/ Screening ⁴	Treatment (Day 1-Day 360)								
						Discharge ²				Endpoint ³
Treatment Day ¹		D1	D2	D3	D5 +1	D9 +2	D30 +7	D90 +7	D180 +14	D360 +14
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9
Informed Consent Form ⁵	X									
Medical History	X									
Vital Signs	X									
Physical Examination	X									
Concomitant medications	X									
Hematology	X									
Coagulation	X									
Biochemistry	X									
Inclusion/Exclusion Criteria		X								
Randomization		X								
Ticagrelor 90mg bid		X	X	X	X	X	X	X	X	X
Aspirin 100mg qd		X	X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X	X
UCG	X							X	X	X
MSCTA ⁶						X				X
Pregnancy Test		X								
Bleeding Events		X	X	X	X	X	X	X	X	X
AEs ⁷		X	X	X	X	X	X	X	X	X

NOTE:

1. CAGB procedure will be operated on Day 0
2. Discharge examination on Day 9±2 may be optional according to each center's routine care.
3. Subject who prematurely terminate treatment for any reason have to complete all the tests listed in the endpoint column. Follow-up duration can be 12 months
4. Investigators must test all the screening results before study drug administration.
5. Informed consent form must be obtained before any study -related procedure.
6. MSCTA: Multislice Computed Tomography Angiography
7. AEs recording began from the signing of informed consent throughout the study until and including the last visit